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Gelation by Histidine-Derived Ureas

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Dedicate to Professor Jerry L. Atwood on the occasion of his 75th Birthday

Introduction

Amides¹⁻⁵ and ureas⁵⁻⁹ are well-known classes of supramolecular gelators, capable of gelling water (hydrogels) and organic solvents (organogels) by means of highly directional NH...O=C hydrogen bonding interactions.¹⁰⁻¹⁶ This type of hydrogen bonded fibre formation is implicated in a range of important biological phenomena such as protein (mis)folding and amyloid formation.¹⁷⁻¹⁸ Gel strength is increased in multifunctional compounds such as bis(amides)¹⁹⁻²¹ and bis(ureas)^{6, 22-23} and the additional NH group in the urea class tends to result in more cohesive materials.²⁴⁻²⁵ Gels consist of extended fibrils²² or scrolled sheets,²⁶ typically comprising continuous arrays of six-membered hydrogen bonded rings known as α -tape motifs.^{9, 27-31} Bunching or braiding of these fibrils gives fibres that entangle to give a three-dimensional sample-spanning gel network capable of immobilising solvent by surface tension effects.¹¹⁻¹² We have recently reported hydrogelation by an imidazole urea (**1**) derived from histamine.³² In this system half of the double α -tape motif of typical bis(urea) gelators is replaced by a zig-zag imidazole NH...N hydrogen bonded chain (Fig. 1). Gelation is

‘turned off’ in this system by interaction with transition metal ions which interrupt the imidazole hydrogen bonding. We now report the organogelation behaviour of a series of related imidazole ureas derived from histidine including substituent dependence and metal responsiveness.

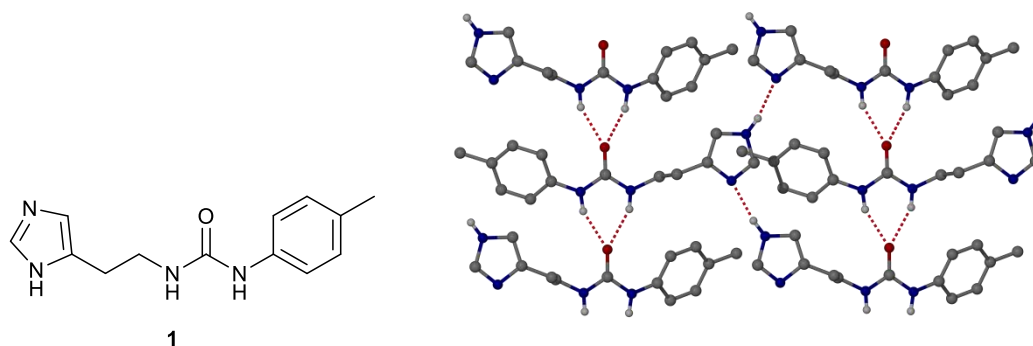


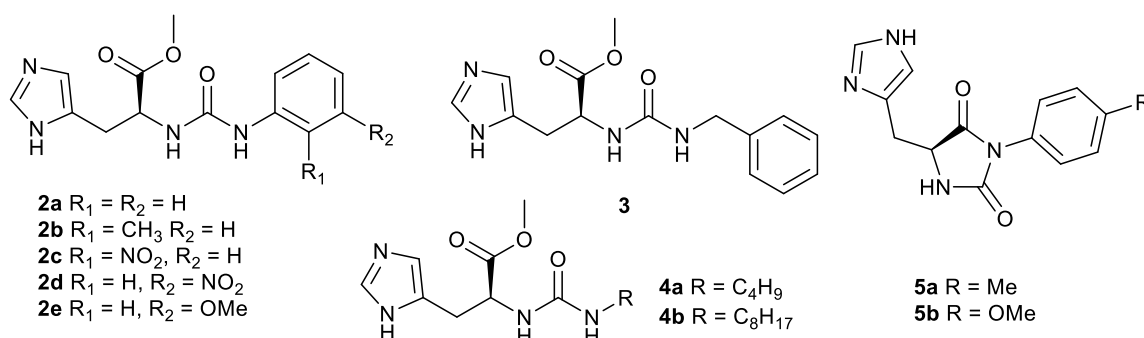
Figure 1. (a) Imidazole urea **1** and (b) its combination of urea α -tape and imidazole NH...N hydrogen bonding.³²

Results and Discussion

Synthesis

The imidazole ureas of types **2** – **4** were prepared in generally good yields by refluxing L-histidine methyl ester dihydrochloride with trimethylamine accompanied by slow addition of the appropriate aryl isocyanate (see experimental section). The *N*-alkyl ureas of type **4** required purification by column chromatography. The aryl ureas of type **2** were found to retain HCl very strongly and were typically obtained as 2:1 hemihydrochloride salts (*vide infra*). Similar reactions with *p*-tolyl and *p*-methoxy isocyanates (which bear electron donating substituents in the para position) gave rise to undesired hydantoin cyclisation products of type **5** which were isolated and

characterised by X-ray crystallography (see supplementary information). Previous studies have suggested the mechanism is a base catalysed ring closure.³³⁻³⁴



Gelation properties

All the compounds were tested across a wide range of different solvents for solubility, gelation ability and tendency to crystallise. Initially, 5 mg of material was weighed in a 2 mL glass vial and 0.5 mL of solvent was added to give 1 % (w/v) mixture. The mixtures were sonicated for approximately 20 seconds to break up large particles and then gently heated until the solid was completely dissolved. Hot solutions were allowed to cool to room temperature. No gelation behaviour was observed for the aryl urea compounds of type **2**. In contrast the benzyl derivative **3** formed organogels in acetonitrile, ethyl acetate, nitromethane and nitrobenzene. In addition, the compound forms a hydrogel immediately upon sonication in water at room temperature.

Ultrasound induced gelation has been reported previously as a useful route to room temperature gelation and in cases of relatively insoluble species may be related to transient dissolution and rapid reprecipitation of surface material.³⁵⁻³⁶ Gels of **3** in nitromethane between 0.5 and 2.0 % (w/v) are stable to the inversion test (Fig. 2a) and partial gels form as low as 0.3 % (w/v) in ethyl acetate (Fig. 2b).

(a)

(b)

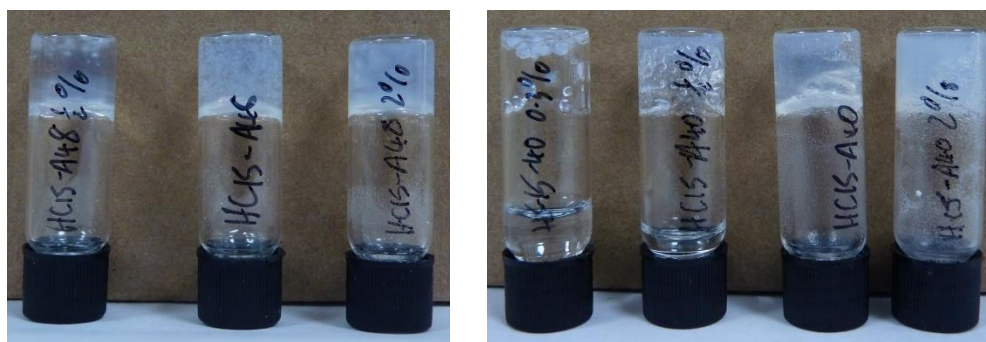


Figure 2. Inversion test of gels of compound **3**. (a) Nitromethane at 0.5, 1 and 2 % (w/v). (b) Ethyl acetate at 0.3, 0.5, 1 and 2 % (w/v).

Xerogels of **3** were investigated by scanning electron microscopy (SEM). Samples were prepared by drying gels of compound **3** obtained from ethyl acetate, nitromethane and water on SEM plates followed by platinum coating. The xerogels comprise long entangled ribbon-like fibres (Fig. 3a).³⁷ The fibres exhibit a helical twist and are homochiral. Helical fibres are commonly observed in xerogels derived from ribbon-like fibres of chiral, racemic and achiral gelators. For example, mixtures of left and right handed helices of gels of achiral **1** have been observed previously.³² Helical twisting can result from variations in mechanical, thermal and/or compositional fields within the crystal growth medium.³⁸ As a solid material precipitates from solution, differences in density and composition increase between the growing solid and the surrounding solution. Twisting can occur if these field variations are significant on either side of the propagating fibre.³⁹ The homochirality of the fibres of the xerogels of **3** are consistent with the use of non-racemic L-histidine derivatives in the present case (Fig 3b). Fig. 3c shows isolated single homochiral helical fibres obtained from the nitromethane gel in addition to a bulk interweaved network, suggesting a long helical persistence length.

SEM images of the dried hydrogel of **3** also show an entangled fibre network comprised of shorter, more bunched fibres (Fig. 3d).

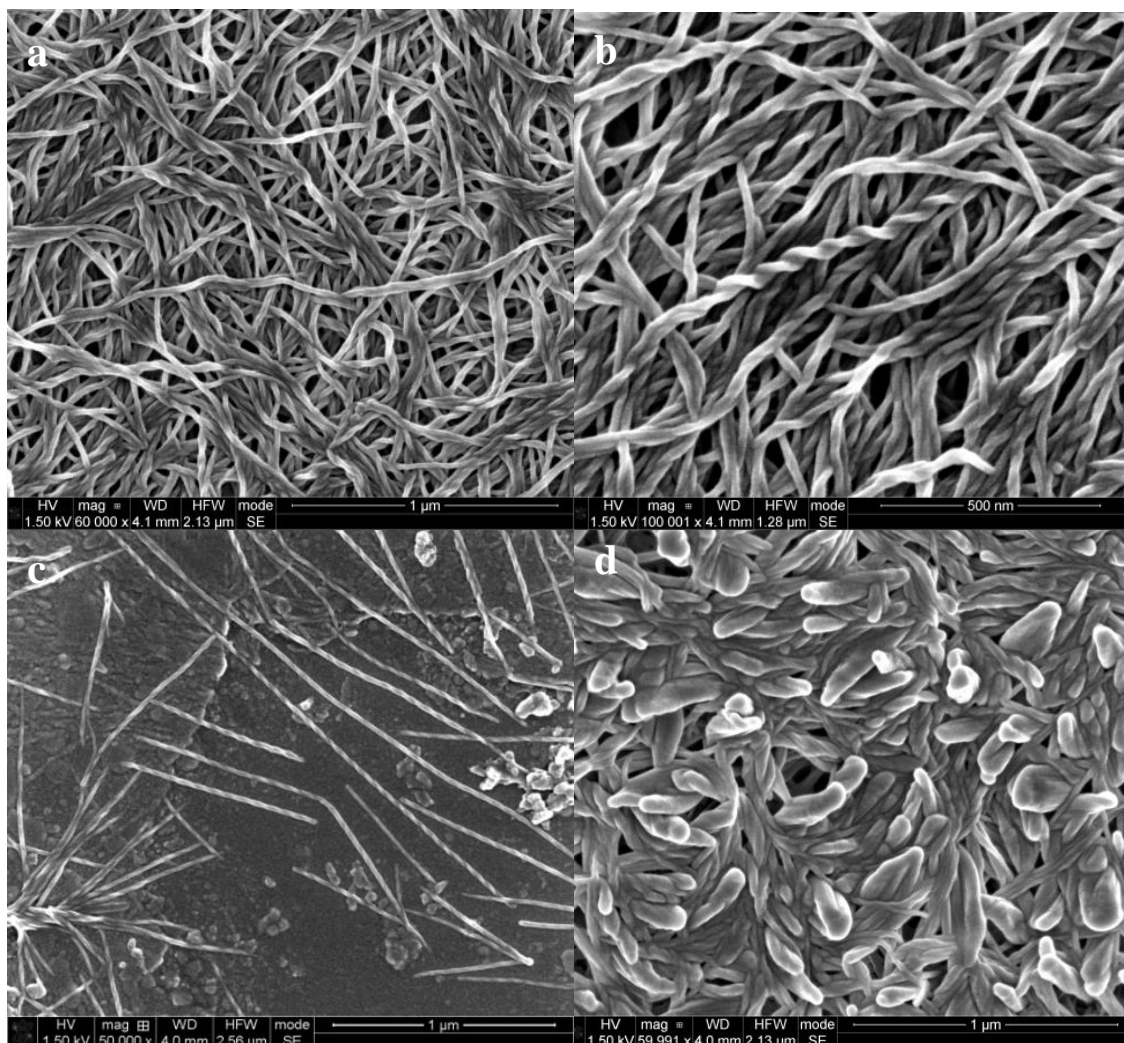


Figure 3. SEM images of xerogels of compound **3** obtained from gels of ethyl acetate (a & b), nitromethane (c) and water (d).

The viscoelastic properties of gels of compound **3** were studied using stress sweep rheometry. Oscillatory stress sweeps of varying gelator concentration were carried out in acetonitrile using a parallel plate rheometer at a gap of 2.5 mm with rough surfaces to improve gel contact. A stress sweep at 1 % (w/v) (Fig. 4) shows that at low stresses, G' is more than an order of magnitude larger than G'' , indicating significant elastic behaviour characteristic of a gel.^{13, 37, 40-41} Viscoelastic behaviour can also be seen by a

slight increase in G'' approaching the yield stress. This weak strain overshoot and commonly due to weak structural interactions between fibres breaking down at high stress.⁴²⁻⁴⁴ Gels generally proved quite rigid with G' increasing from around 20,000 Pa at 0.5 % w/v to 1.35×10^5 Pa at 1.7 % w/v with yield stress increasing from 500 – 2000 Pa over the same concentration range (see supplementary information Fig. S1).

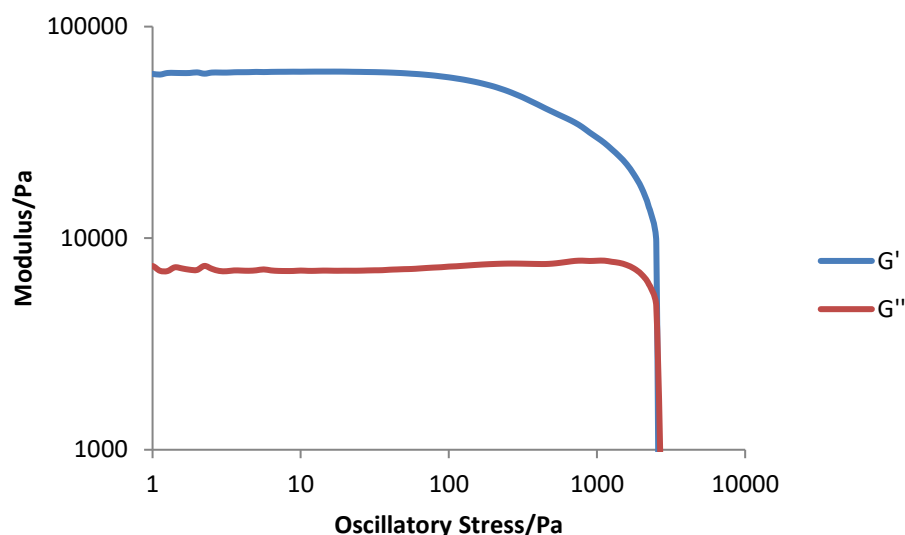


Figure 4. Oscillatory stress sweep of 1 % (w/v) of an acetonitrile gel of **3**.

The alkyl ureas of type **4** also proved to be effective gelators. The butyl derivative **4a** formed weak gels in chloroform, dichloromethane, and nitrobenzene at 1 % w/v. The SEM images of nitrobenzene xerogels of this compound differ considerably from **3** and show a mixture of thin twisted fibrils and wider, flat ribbon structures (Fig. 5). No evidence of helical twisting is apparent despite the chirality of the gelator. The wider plate-like structures are less common in gels and suggest that the material is relatively crystalline with a much longer persistence length (the distance for a fibre to loop back on itself) than reported previously for fibrous structures such as DNA (50 nm) and gelatin B (2 nm).⁴⁵

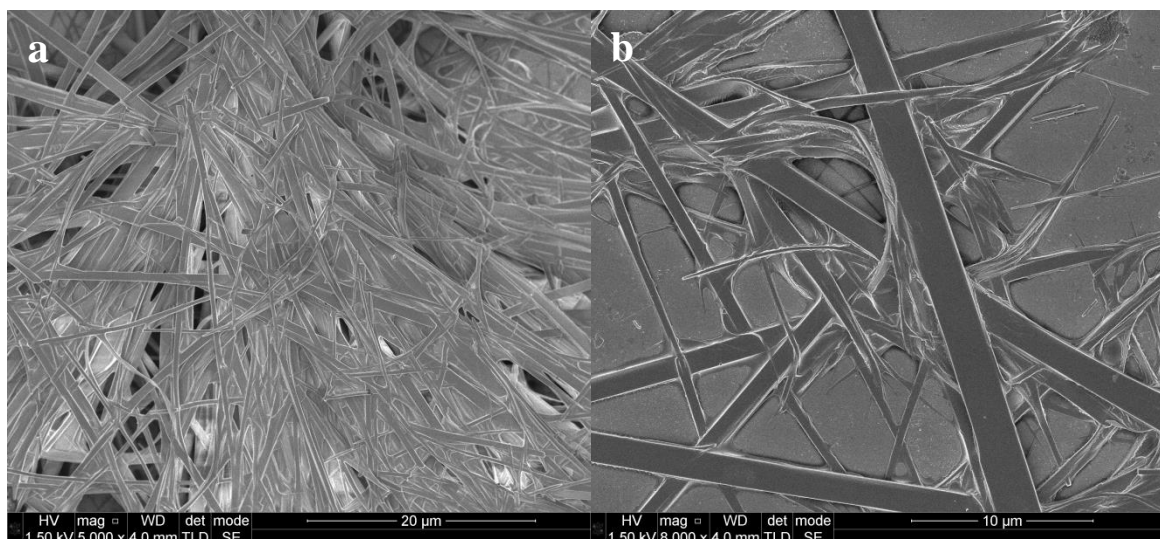


Figure 5. SEM images of xerogels of compound **4a** dried from gels of nitrobenzene. (a) Network of interwoven ribbons and ribbons. (b) Detail of individual ribbons.

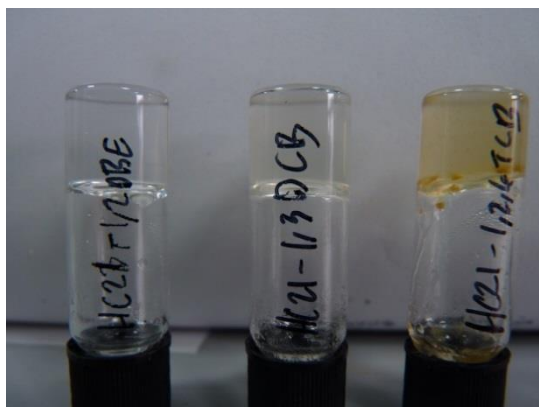


Figure 6. Inversion test of gels of compound **4b** at 1 % (w/v) in 1,2-dibromoethane, 1,3-dichlorobenzene and 1,2,4-trichlorobenzene.

In contrast the octyl analogue, **4b**, formed transparent robust gels in several solvents, namely 1,2-dibromoethane, 1,3-dichlorobenzene and 1,2,4-trichlorobenzene at 1 % (w/v) (Fig. 6). Weak gels also formed in chloroform, dichloromethane and nitrobenzene. The gel of **4b** in 1,3-dichlorobenzene at 1 % (w/v) was investigated by oscillatory stress sweep rheometry (see supplementary information Fig. S2) which

demonstrates it to be of similar strength of the acetonitrile gel of **3**. Also, as with **3**, viscoelastic behaviour occurs approaching the yield point. This behaviour is illustrated by a marked increase in G'' due to weak structural interactions between fibres breaking down at high stress. SEM of xerogels of **4b** revealed a helical, entangle structure more similar to xerogels of **3** than **4a**. SEM images show an intertwined network of thin fibrils expected for a gel (Fig. 6a).¹ The fibrils are twisted with the same handedness throughout the network as anticipated due to the chirality of the gelator molecule. Individual twisted fibrils are also shown to wrap around each other to form larger braided structures (Fig. 6b).¹¹

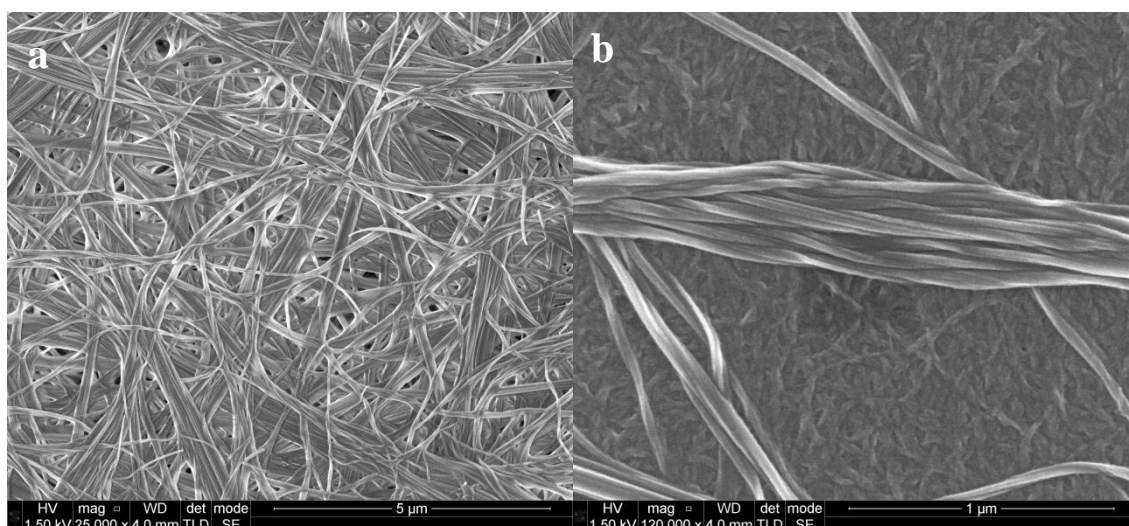


Figure 6. SEM images of xerogels of compound **4b** dried from gels of 1,3-dichlorobenzene. (a) network of interwoven fibres. (b) Showing twisted fibres of the same handedness.

Reports have previously outlined that the presence of long alkyl chains facilitate gelation, whereas the presence of short alkyl chains or branching favours solubilisation or crystallization.⁴⁶ The gelation behaviour of the alkyl analogues of type **4** are consistent with this observation with **4a** being a poorer gelator and forming more crystalline aggregates than the octyl analogue **4b**.

It is interesting that while the sterically unhindered ureas **3** and **4b** are quite effective gelators, the aryl ureas of type **2** are ineffective in gel formation. This observation may be linked to the formation of intramolecular CH...O hydrogen bonds between the aryl CH groups and the urea carbonyl oxygen atom. This well-reported effect²⁹⁻³⁰ results in considerable steric hindrance of the urea carbonyl and consequent decrease in its hydrogen bond basicity. As a result it is likely that the urea α -tapes are either not formed in the case of compounds of type **2** or are too weak to result in effective fibril formation.

Metal and Halide Complexation

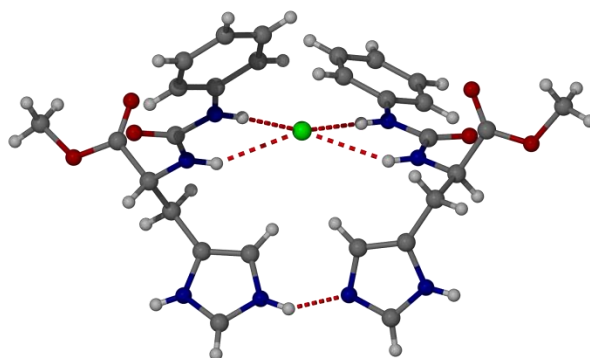
Complexation of imidazole urea **1** with transition metal ions results in a marked decrease in its gelation ability and the competing formation of a range of metal complexes.³² In contrast, pyridyl ureas are strengthened by metal complexation,⁴⁷ while pyridinyl methyl species exhibit complex responsive behaviour.⁴⁸ The behaviour of gelator **3** parallels that of **1**. Compound **3** was screened across a range of metal salts to investigate if the gelator molecule could coordinate metal ions to produce a metallogel. The metal salts studies were nickel(II) chloride, nickel(II) nitrate, cobalt(II) chloride, cobalt(II) nitrate, copper(II) chloride, copper(II) nitrate, iron(III) chloride and zinc(II) nitrate. At a 1:1 ratio of gelator to metal ion in acetonitrile and methanol, the gelator remained in solution. Upon sonication a gel formed with cobalt(II) chloride and **3** in acetonitrile at very low metal to gelator ratios. At 1:0.05 molar ratio of salt to **3** a gel formed, while at 1:0.2 a partial gel formed (supplementary information Fig. S3). Partial metallogels were also noted with copper(II) chloride and cobalt(II) nitrate. Since gels only form at very low metal to gelator ratios it is suggested that the metals inhibit gel

formation by complexation of the imidazole functionality and hence interruption of the imidazole NH...N interactions as well as by hydrogen bonding of the urea NH groups to the counter anions.

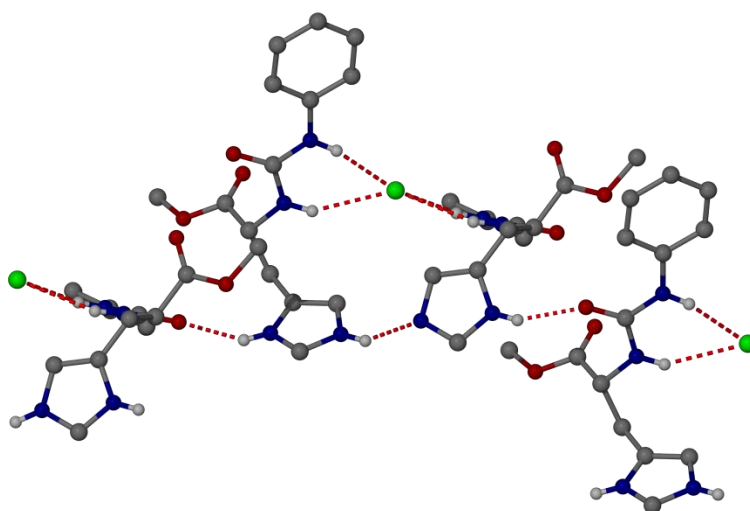
Compounds of type **2** retain chloride extremely strongly as hemihydrochloride salts. Single crystal structures were obtained for the phenyl derivative **2a**·0.5HCl in both unsolvated form and as an acetonitrile solvate **2a**·0.5HCl·2MeCN. Single crystal structures were also obtained for hemihydrochlorides **2b**·0.5HCl·0.25NO₂Me, **2d**·0.5HCl·MeCN and for **2e** as a monohydrochloride, **2e**·HCl·3NO₂Me.

Both the solvated and non-solvated hemihydrochloride forms of **2a** are based on hydrogen bonded sandwich pairs (Fig. 7a) in which one protonated and one non-protonated molecule of **2a** are linked via a chloride ion sandwiched between urea groups and a imidazolium to imidazole NH...N hydrogen bond groups. Within this unit, the four NH groups of the two urea moieties hydrogen bonds to the chloride ion to form a distorted tetrahedral geometry with N...Cl distances of 3.311(2) and 3.233(2) Å in **2a**·0.5HCl·2MeCN, for example. The proton is shared between the hydrogen bond acceptor nitrogen atoms of imidazole groups to create an N-H-N interaction within each dimer with N...N distance of 2.671(4) Å. The crystal structure comprises hydrogen bond tapes with a chloride-urea-imidazole-imidazole-urea repeat unit (Fig. 7b). The tape involves hydrogen bonding between the chloride ion and the NH group of the urea dimer interaction followed by hydrogen bonding between the CO of the urea of one sandwich unit and the NH group of the imidazole of the next sandwich in the tape to create a CO...H-N interaction with O...N distance of 2.760(3) Å in **2a**·0.5HCl·2MeCN. The tape continues with hydrogen bonding between adjacent imidazole molecules and proton N-H-N interaction with N...N distance of 2.671(4) Å. The NH group of the imidazole is then linked to the CO of urea of the next molecule via hydrogen bonds. The

two NH groups of the urea form hydrogen bonds to the next chloride ion, and the tape continues in the same way. These tapes differ from classic urea α -tapes as they incorporate urea-chloride, urea-imidazole and imidazole-imidazole interactions. The unsolvated **2a**·0.5HCl isolated from nitromethane and the structures of **2b**·0.5HCl·0.25NO₂Me, **2d**·0.5HCl·MeCN are approximately isostructural to **2a**·0.5HCl·2MeCN and are based on the same chain of sandwich complexes. In every case the aryl substituent is coplanar with the urea moiety and the urea carbonyl group is partially hindered by intramolecular CH \cdots O interactions, reducing its hydrogen bond acceptor ability. This relative inaccessibility might contribute to the superior gelation properties of the less hindered analogues of types **3** and **4**.



(a)



(b)

Figure 7. X-ray crystals structure of **2a**·0.5HCl·2MeCN: (a) chloride sandwich unit and (b) extended hydrogen bonded chain (CH atoms omitted for clarity).

The structure of the monohydrochloride **2e**·HCl·3NO₂Me is shown in Fig. 8. The different stoichiometry results in a different structure in which each of the two symmetry-independent ($Z' = 2^{49}$) chloride ions forms symmetrical hydrogen bonds to the two urea NH groups of a protonated ligand, NH···Cl 3.234(4) Å (av.) along with an imidazolium NH group, NH···Cl 3.073(4) Å. As in the other structures the urea carbonyl group accepts hydrogen bonds from the other imidazolium NH group, NH···O=C 2.685(5) Å. Despite the electron donating OMe group the aryl substituent is still almost coplanar with the urea moiety (torsion angle 22° and hence the urea carbonyl remains sterically hindered).

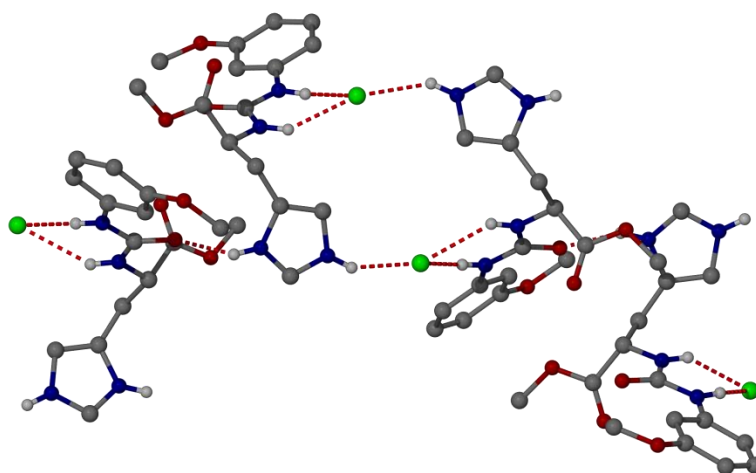


Figure 8. X-ray crystal structure of **2e**·HCl·3NO₂Me

Conclusions

Imidazole monoureas derived from non-racemic L-histidine are effective organogelators in cases where the urea bears aliphatic groups immediately adjacent to the nitrogen

atoms. As with the related histamine derivatives³² helical twisted fibres are observed, but the presence of the resolved asymmetric centre results in all fibres having the same handedness. Aryl ureas are not effective gelators as a result of the steric hindrance of the urea carbonyl group and instead the urea NH groups display a strong tendency to retain chloride as the hydrochloride salts, generally forming sandwich-type hemihydrochlorides. As with histamine-derived imidazole ureas, transition metal ion complexation results in gelation ‘turn-off’ further increasing the scope of these versatile and responsive soft materials.¹⁰

Experimental

Crystallography

The X-ray single crystal data for compounds **2a**·0.5HCl, **2b**, **2d** and **5a** were collected on a Bruker D8 Venture (Photon100 CMOS detector, I μ S-microsource, focusing mirrors, λ CuK α , λ = 1.54173 Å) and for compounds **2a** and **5b** on a Agilent XCalibur (Sapphire-3 CCD detector, fine-focus sealed tube, graphite monochromator, λ MoK α , λ = 0.71073 Å) diffractometers equipped with a Cryostream (Oxford Cryosystems) open-flow nitrogen cryostats at the temperature 120.0(2) K. The data for compound **2e** were collected at 100 K on a Rigaku Saturn 724+ diffractometer at station I19 of the Diamond Light Source synchrotron (undulator, λ = 0.6889 Å, ω -scan, 1.0°/frame) and processed using Bruker APEXII software. All structures were solved by direct method and refined by full-matrix least squares on F^2 for all data using Olex2⁵⁰ and SHELXTL⁵¹ software. All non-disordered non-hydrogen atoms were refined anisotropically, hydrogen atoms were placed in the calculated positions and refined in riding mode. Crystal data and parameters of refinement are listed in the experimental section. Crystallographic data for the structure have been deposited with the Cambridge Crystallographic Data Centre

as supplementary publication CCDC-1560227-1560233.

Synthesis

1-[2-(1H-imidazol-4-yl)ethyl]-(2-methylester)-3-phenylurea (2a)

A stirred solution of L-histidine methyl ester dihydrochloride (0.500 g, 2.07 mmol) in chloroform (50 mL) and triethylamine (0.58 mL, 4.13 mmol) was heating to reflux under flowing nitrogen. A solution of phenyl isocyanate (0.246 g, 2.07 mmol) in chloroform (10 mL) was slowly added via the dropping funnel over 1 hour, before refluxing for 18 hours. The resulting white precipitate was filtered under vacuum, washed with chloroform (3 x 20 mL) and water (3 x 20 mL) then dried under vacuum in a drying pistol to yield the product as a white powder (0.293 g, 1.02 mmol, 49%); CHN anal. found: C, 52.76; H, 4.73; N, 18.19. Calc. for $C_{14}H_{16}N_4O_3 \cdot 0.8HCl$: C, 52.97; H, 5.33; N, 17.65%; IR ν / cm^{-1} 3118 (NH), 3000 (CH), 1700 (CO), 1502 (C=C), 1422 (CN); δ_H (400 MHz; DMSO) 9.04 (1H, s, *NH*), 8.29 (1H, s, *Imid*), 7.36 (2H, d, *J* 8.0, *ArH*), 7.21 (2H, t, *J* 7.8, *ArH*), 7.18 (1H, s, *Imid*), 6.90 (1H, t, *J* 7.3, *ArH*), 6.77 (1H, d, *J* 7.8, *NH*), 4.55 (1H, td, *J*₁ 7.6, *J*₂ 5.3, *CH*), 3.65 (3H, s, *CH*₃), 3.11 – 2.95 (2H, m, *CH*₂); δ_C (101 MHz, DMSO) 172.75, 155.14, 140.58, 134.90, 131.72, 129.12, 121.75, 118.05, 117.17, 79.67, 52.57, 28.71; *m/z* (ESI-MS) 289 [M+H]⁺.

Recrystallisation from acetonitrile yielded single crystals of $2a \cdot \frac{1}{2}HCl$ as an acetonitrile solvate. *Crystal data*: $C_{32}H_{39}ClN_{10}O_6$, *M* = 695.18, monoclinic, space group I2, *a* = 12.6530(8), *b* = 8.1354(4), *c* = 16.9922(9) Å, β = 92.098(5)°, *U* = 1747.96(17) Å³, *F*(000) = 732, *Z* = 2, *D*_c = 1.321 mg m⁻³, μ = 0.167 mm⁻¹, *T* = 120(1)K. 15951 reflections were collected yielding 4657 unique data (*R*_{merg} = 0.0797). Final *wR*₂(*F*²) = 0.1198 for all data (248 refined parameters), conventional *R*₁(*F*) = 0.06187 for 3354 reflections with *I* ≥ 2σ, *GOF* = 1.027.

Recrystallisation from nitromethane yielded single crystals of **2a**· $\frac{1}{2}$ HCl. *Crystal data*: C₂₈H₃₃ClN₈O₆, M = 613.07, monoclinic, space group C2, a = 20.5259(8), b = 8.1162(3), c = 12.4178(5) Å, β = 124.638(2)°, U = 1702.05(12) Å³, F(000) = 644, Z = 2, D_c = 1.196 mg m⁻³, μ = 1.409 mm⁻¹, T = 120(1)K. 9714 reflections were collected yielding 3020 unique data (R_{merg} = 0.0391). Final wR₂(F²) = 0.1082 for all data (221 refined parameters), conventional R₁(F) = 0.0466 for 2786 reflections with I ≥ 2σ, GOF = 1.076.

1-[2-(1H-imidazol-4-yl)ethyl]-(2-methylester)-3-(2-tolyl)urea (2b)

A stirred solution of L-histidine methyl ester dihydrochloride (1.00 g, 4.13 mmol) in chloroform (100 mL) and triethylamine (1.16 mL) was heated to reflux under nitrogen. O-tolyl isocyanate (0.550 g, 4.130 mmol) was added before refluxing for 18 hours. The resulting white precipitate was filtered and dried under vacuum in a drying pistol to yield the product as a white powder (1.140g, 3.97 mmol, 96%); CHN anal. found: C, 49.16; H, 5.06; N, 14.90. Calc. for C₁₅H₁₈N₄O₃·1.8HCl: C, 48.96; H, 5.42; N, 15.23%; ν_{max}/cm⁻¹ 3256 (NH), 3160 (NH), 3022 (CH), 1679 (CO), 1543 (C=C), 1454 (CN); δ_H (400 MHz; DMSO) 12.80 (1H, br s, *NH*), 8.30 (1H, d, *J* 1.2, *Imid*), 8.06 (1H, s, *NH*), 7.73 (1H, dd, *J*₁ 8.1, *J*₂ 1.2, *ArH*), 7.22 (1H, d, *J* 7.8, *NH*), 7.18 (1H, d, *J* 1.2, *Imid*), 7.14-7.10 (1H, m, *ArH*), 7.08 (1H, td, *J*₁ 7.8, *J*₂ 1.2 *ArH*), 6.88 (1H, td, *J*₁ 7.4, *J*₂ 1.2, *ArH*), 4.56 (1H, td, *J*₁ 7.8, *J*₂ 5.4, *CH*), 3.65 (3H, s, *CH*₃), 3.12 – 2.95 (2H, m, *CH*₂), 2.18 (3H, s, *CH*₃); δ_C (101 MHz, DMSO) 172.80, 155.38, 138.26, 134.82, 131.53, 130.54, 127.65, 126.45, 122.68, 121.19, 117.37, 52.85, 52.44, 28.86, 18.51; m/z (ESI-MS) 302 [M]⁺, 627 [2M+Na]⁺.

Recrystallisation from nitromethane yielded single crystals of **2b**· $\frac{1}{2}$ HCl as a nitromethane solvate. *Crystal data*: C₃₀H₃₇ClN₈O₆ x 0.5CH₃NO₂, M = 671.65, monoclinic, space group C2, a = 20.8478(7), b = 8.0860(3), c = 12.3738(4) Å, β = 124.119(2)°, U = 1726.87(10) Å³, F(000) = 708, Z = 2, D_c = 1.292 mg m⁻³, μ = 1.460

mm⁻¹, T = 120(1)K. 9946 reflections were collected yielding 3073 unique data ($R_{\text{merg}} = 0.0498$). Final $wR_2(F^2) = 0.1676$ for all data (215 refined parameters), conventional $R_1(F) = 0.0589$ for 2641 reflections with $I \geq 2\sigma$, GOF = 1.123.

1-[2-(1H-imidazol-4-yl)ethyl]-(2-methylester)-3-(2-nitrophenyl)urea (2c)

A stirred solution of L-histidine methyl ester dihydrochloride (1.00 g, 4.13 mmol) in chloroform (100 mL) and triethylamine (1.16 mL) was heated to reflux under nitrogen. O-nitrophenyl isocyanate (0.678 g, 4.13 mmol) was added before refluxing for 18 hours. The resulting yellow solution was washed with water and yellow solid precipitated out into the chloroform. This precipitate was filtered and dried under vacuum in a drying pistol to yield the product as a powder (0.365g, 1.12 mmol, 27 %); CHN anal. found: C, 50.39; H, 4.34; N, 21.32. Calc. for C₁₄H₁₅N₅O₅: C, 50.45; H, 4.54; N, 21.01%; IR ν / cm⁻¹: 3266 (NH), 2958 (CH), 1741 (CO), 1599 (C=C), 1422 (CN); δ_{H} (400 MHz; DMSO) 11.86 (1H, br s, *NH*), 9.48 (1H, s, *Imid*), 8.21 (1H, d, *J* 8.6, *ArH*), 8.08-7.98 (1H, m, *ArH*), 7.87 (1H, m, *NH*), 7.63 (1H, ddd, *J*₁ 8.7, *J*₂ 7.1, *J*₃ 1.7, *ArH*), 7.56 (1H, s, *Imid*), 7.15 (1H, ddd, *J*₁ 8.4, *J*₂ 7.2, *J*₃ 1.4, *ArH*), 6.90 (1H, s, *NH*), 4.49 (1H, d, *J* 6.9, *CH*), 3.63 (3H, s, *CH*₃), 3.01 – 2.81 (2H, m, *CH*₂); δ_{C} (101 MHz, DMSO) 173.00, 154.85, 154.44, 137.89, 135.56, 135.40, 135.26, 125.72, 122.72, 122.28, 113.84, 53.66, 52.31, 30.73; m/z (ESI-MS) 334 [M]⁺, 335 [M+H]⁺.

1-[2-(1H-imidazol-4-yl)ethyl]-(2-methylester)-3-(3-nitrophenyl)urea (2d)

A stirred solution of L-histidine methyl ester dihydrochloride (1.00 g, 4.13 mmol) in chloroform (100 mL) and triethylamine (1.16 mL) was heated to reflux under nitrogen. M-nitrophenyl isocyanate (0.678 g, 4.13 mmol) was added before refluxing for 18 hours. The resulting yellow precipitate was filtered and dried under vacuum in a drying pistol to yield the product as a powder (0.886g, 2.64 mmol, 64 %); CHN anal. found: C,

42.96; H, 3.96; N, 17.48. Calc. for $C_{14}H_{15}N_5O_5 \cdot 1.6HCl$: C, 42.94; H, 4.27; N, 17.88%; IR ν / cm^{-1} 3263 (NH), 3058 (NH), 3022 (CH), 1690 (CO), 1528 (C=C), 1436 (CN); δ_H (400 MHz; DMSO) 11.88 (1H, br s, *NH*), 9.64 (1H, s, *NH*), 8.49 (1H, d, *J* 2.2, *ArH*), 8.30 (1H, d, *J* 1.2, *Imid*), 7.77 (1H, ddd, *J*₁ 8.1, *J*₂ 2.4, *J*₃ 1.0, *ArH*), 7.62 (1H, ddd, *J*₁ 8.2, *J*₂ 2.2, *J*₃ 1.0, *ArH*), 7.51 (1H, t, *J* 8.2, *ArH*), 7.19 (1H, d, *J* 1.2, *Imid*), 6.98 (1H, d, *J* 7.8, *NH*), 4.58 (1H, td, *J*₁ 7.6, *J*₂ 5.4, *CH*), 3.66 (3H, s, *CH*₃), 3.12 – 3.01 (2H, m, *CH*₂); δ_C (101 MHz, DMSO) 172.43, 154.96, 148.57, 141.89, 134.96, 131.73, 130.44, 124.09, 117.07, 116.25, 111.92, 52.73, 52.56, 28.46; *m/z* (ESI-MS) 334 [M+H]⁺.

Recrystallisation from acetonitrile yielded single crystals of $2d \cdot \frac{1}{2}HCl$ as an acetonitrile solvate. *Crystal data*: $C_{30}H_{34}ClN_{11}O_{10}$, *M* = 744.13, monoclinic, space group *P*2₁, *a* = 8.0878(5), *b* = 20.3015(11), *c* = 11.4502(7) Å, β = 110.867(3)°, *U* = 1756.75(18) Å³, *F*(000) = 776, *Z* = 2, *D*_c = 1.407 mg m⁻³, μ = 1.583 mm⁻¹, *T* = 120(1)K. 20210 reflections were collected yielding 6403 unique data (*R*_{merg} = 0.0395). Final *wR*₂(*F*²) = 0.0900 for all data (586 refined parameters), conventional *R*₁(*F*) = 0.0382 for 6009 reflections with *I* ≥ 2σ, *GOF* = 1.052.

1-[2-(1H-imidazol-4-yl)ethyl]-(2-methylester)-3-(3-methoxyphenyl)urea (2e)

A stirred solution of L-histidine methyl ester dihydrochloride (0.500 g, 2.07 mmol) in chloroform (50 mL) and triethylamine (0.58 mL) was heated to reflux under nitrogen. 3-methoxyphenyl isocyanate (0.308 g, 2.07 mmol) was added before refluxing for 18 hours. The resulting white precipitate was filtered and dried under vacuum in a drying pistol to yield the product as a white powder (0.510g, 1.62 mmol, 78%); CHN anal.(Found: C, 50.11; H, 5.12; N, 15.69. Calc. for $C_{15}H_{18}N_4O_4 \cdot HCl$: C, 50.78; H, 5.40; N, 15.79%); ν_{max}/cm^{-1} 3266 (NH), 2958 (CH), 1741 (CO), 1599 (C=C), 1422 (CN); δ_H (400 MHz; DMSO) 13.36 (1H, br s, *NH*), 8.98 (1H, s, *NH*), 8.29 (1H, d, *J* 1.2, *Imid*), 7.17 (1H, d, *J* 1.2, *Imid*), 7.15-7.08 (2H, m, *ArH*), 6.84 (1H, ddd, *J*₁ 8.2, *J*₂ 2.0, *J*₃ 0.9, *ArH*), 6.74 (1H, d, *J* 7.8, *NH*), 6.84 (1H, ddd, *J*₁ 8.2, *J*₂ 2.5, *J*₃ 0.9, *ArH*), 4.55 (1H, td, *J*₁

7.8, J_2 5.4, CH), 3.65 (3H, s, CH₃), 3.51 (3H, s, CH₃), 3.16 – 2.87 (2H, m, CH₂); δ_C (101 MHz, DMSO) 172.69, 160.08, 155.04, 141.79, 134.90, 131.69, 129.86, 117.13, 110.43, 107.18, 103.84, 55.31, 52.61, 52.48, 28.67; m/z (ESI-MS) 319.1 [M+H]⁺.

Recrystallisation from nitromethane yielded single crystals of **2e**·HCl·3NO₂Me. *Crystal data*: C₁₅H₁₉ClN₄O₄ x 1.5 CH₃NO₂, M = 446.36, orthorhombic, space group P2₁2₁2₁, a = 8.136(2), b = 21.398(6), c = 24.347(7) Å, U = 4238(2) Å³, F(000) = 1872, Z = 8, D_c = 1.399 mg m⁻³, μ = 0.213 mm⁻¹, T = 100(1)K. 24740 reflections were collected yielding 7403 unique data (R_{merg} = 0.0765). Final $wR_2(F^2)$ = 0.1870 for all data (546 refined parameters), conventional $R_1(F)$ = 0.0782 for 5832 reflections with $I \geq 2\sigma$, GOF = 1.129.

1-[2-(1H-imidazol-4-yl)ethyl]-(2-methylester)-3-benzylurea (3)

A stirred solution of L-histidine methyl ester dihydrochloride (0.50 g, 2.07 mmol) in chloroform (50 mL) and triethylamine (0.58 mL, 4.13 mmol) was heating to reflux under flowing nitrogen. A solution benzyl isocyanate (0.275 g, 2.07 mmol) in chloroform (10 mL) was slowly added via the dropping funnel over 1 hour, before refluxing for 18 hours. The resulting white precipitate was filtered under vacuum, washed with chloroform (3 x 20 mL) and water (3 x 20 mL) then dried under vacuum in a drying pistol to yield the product as a white powder(0.293 g, 0.940 mmol, 46%); CHN anal. found: C, 59.36; H, 5.97; N, 18.29. Calc. for C₁₅H₁₈N₄O₃: C, 59.59; H, 6.00; N, 18.53%; IR ν / cm⁻¹ 3371 (NH), 3366 (NH), 3089 (CH), 1734 (CO), 1621 (NH imid.), 1557 (NH imid.), 1437 (CN); δ_H (400 MHz; DMSO) 11.88 (1H, br s, NH), 7.57 (1H, s, Imid), 7.31 (2H, t, J 7.5, ArH), 7.26 – 7.18 (3H, m, ArH), 6.81 (1H, s, Imid), 6.72 (1H, t, J 5.9, NH), 6.30 (1H, d, J 8.0, NH) 4.44 (1H, td, J_1 6.8, J_2 6.8, CH), 4.18 (2H, d, J 5.9, CH₂), 3.60 (3H, s, CH₂), 2.88 (2H, d, J 6.3, CH₂); δ_C (101 MHz, DMSO) 173.56, 157.95, 141.07, 135.35, 133.77, 128.66, 127.42, 127.02, 116.89, 53.40, 52.10, 43.25, 30.16; m/z (ESI-MS) 302 [M]⁺, 605 [2M+H]⁺, 627 [2M+Na]⁺, 196, 170, 102.

1-[2-(1H-imidazol-4-yl)ethyl]-(2-methylester)-3-Butylurea (4a)

A stirred solution of L-histidine methyl ester dihydrochloride (1.00 g, 4.13 mmol) in chloroform (100 mL) and triethylamine (1.16 mL) was heated to reflux under nitrogen. Butyl isocyanate (0.409 g, 4.13 mmol) was added before refluxing for 18 hours. The reaction mixture was reduced to 20% solution and left to evaporate. The yellow precipitate was then purified by column chromatography to yield the product as a yellow solid (0.136 g, 0.500 mmol, 12 %); CHN anal. found: C, 51.21; H, 8.78; N, 16.62. Calc. for $C_{12}H_{20}N_4O_3 \cdot 2MeOH$: C, 50.59; H, 8.49; N, 16.86%; IR ν / cm^{-1} 3329 (NH), 2954 (CH), 1735 (CO), 1624 (NH imid.), 1563 (NH imid.), 1436 (CN); δ_H (400 MHz; DMSO) 11.00 (1H, s, *NH*), 7.63 (1H, d, *J* 1.2, *Imid*), 6.83 (1H, d, *J* 1.2, *Imid*), 6.21 (1H, t, *J* 5.6, *NH*), 6.17 (1H, d, *J* 8.0, *NH*), 4.39 (1H, td, *J*₁ 7.9, *J*₂ 6.3, *CH*), 3.58 (3H, s, *CH*₃), 2.94 (2H, q, *J* 6.4, *CH*₂), 2.85 (2H, d, *J* 6.4, *CH*₂), 1.38-1.28 (2H, m, *CH*₂), 1.29-1.23 (2H, m, *CH*₂), 0.86 (3H, t, *J* 7.1, *CH*₃); δ_C (101 MHz, DMSO) 173.60, 157.86, 135.22, 53.24, 52.05, 39.86, 32.48, 30.02, 19.95, 14.16, 8.95; m/z (ESI-MS) 269 [M+H]⁺.

1-[2-(1H-imidazol-4-yl)ethyl]-(2-methylester)-3-octylurea (4b)

A stirred solution of L-histidine methyl ester dihydrochloride (0.50 g, 2.065 mmol) in chloroform (50 mL) and triethylamine (0.58 mL) was heated to reflux under nitrogen. Octyl isocyanate (0.321 g, 2.065 mmol) was added before refluxing for 18 hours. The reaction mixture was reduced to 20% solution and left to evaporate to yield a white precipitate. This was then purified by column chromatography to yield the product as a white solid (0.346 g, 1.07 mmol, 26 %); CHN anal. found: C, 60.04; H, 8.79; N, 16.44. Calc. for $C_{16}H_{28}N_4O_3$: C, 59.24; H, 8.70; N, 17.27 %; IR ν / cm^{-1} : 3332 (NH), 2928 (CH), 1734 (CO), 1624 (NH), 1561 (NH imid.), 1435 (CN); δ_H (400 MHz; DMSO)

11.95 (1H, s, *NH*), 7.85 (1H, s, *Imid*), 6.80 (1H, s, *Imid*), 6.18 (1H, t, *J* 5.6, *NH*), 6.11 (1H, d, *J* 8.1, *NH*), 4.39 (1H, td, *J*₁ 8.0, *J*₂ 6.2, *CH*), 3.58 (3H, s, *CH*₃), 2.93 (2H, q, *J* 6.7, *CH*₂), 2.85 (2H, d, *J* 6.3, *CH*₂), 1.37-1.20 (12H, m, *CH*₂), 0.90-0.82 (3H, m, *CH*₃); δ_c (101 MHz, DMSO) 173.63, 157.84, 135.29, 53.26, 52.03, 39.70, 31.71, 30.36, 29.22, 29.17, 26.84, 22.56, 14.43; *m/z* (ESI-MS) 325 [*M*+*H*]⁺.

Acknowledgements

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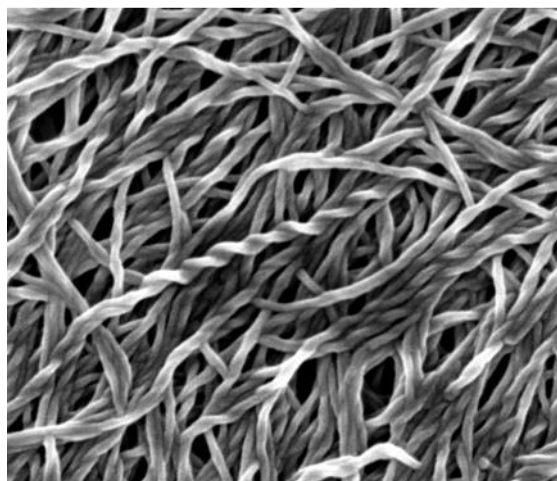
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Gelation by Histidine-Derived Ureas

Graphical Abstract



A series of L-histidine-derived monoureas are described which exhibit versatile organogelation properties when the substituent directly attached to the urea is an aliphatic group. Arylureas exhibit a tendency to bind chloride anion.

Keywords: gel, urea, imidazole, hydrogen bonding